D-dimer levels predict COVID-19 severity and mortality

To the editor   We read with great interest the expert opinion by Kałużna-Oleksy et al,[1] which is a synthetic summary of the current knowledge on the various aspects of heart failure in patients with coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has forced a search for new markers of disease severity. D-dimers are the breakdown products of fibrin fibers. The increased concentration of D-dimer in blood shows the ongoing formation of a fibrin clot and subsequent fibrinolysis process, which are features of venous thromboembolism and other diseases related to the hypercoagulatory state.[2] D-dimer testing is used to identify patients who are at high risk of thromboembolism and therefore require anticoagulation treatment.[3,4] In the current COVID-19 pandemic, the search for early markers of the severity of the COVID-19 course is crucial. As shown by Shau et al[5] and Szarpak et al,[6] lactate dehydrogenase can be such a predictor. Ribes et al[7] showed that the severe form of COVID-19 rapidly grows towards a systemic inflammatory storm with vascular changes in multiple organs, particularly in the lungs and central nervous system. In order to verify the usefulness of D-dimer concentration as a predictor of the severity of the patient's condition, we decided to conduct a systematic review and meta-analysis.

Three authors (LS, MP, and MJJ) searched electronic resources (MEDLINE, MEDLINE in process, Embase, Cochrane Library for clinical trials, PubMed, Web of Science, SCOPUS) from the inception to November 10, 2020 using the following query: *D-dimer* AND *COVID-19* OR *SARS-CoV-2* OR *coronavirus*. A review of the bibliographies of the relevant articles was also performed. Two independent investigators (JS and LS) screened the titles and abstracts of the retrieved articles. The key search words were: *D-dimer** AND *COVID-19* OR *SARS-CoV-2* OR *coronavirus*.

We present all results with their 95% confidence intervals (CIs). When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and SDs using the formula described by Hozo. The random-effects model was used for I^2 greater than 50%. A *P* value of less than 0.05 was considered statistically significant. Statistical testing was 2-tailed. All the above analyses were presented using RevMan5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark).

A total of 23 studies including 3423 patients reported D-dimer levels in patients with severe and nonsevere COVID-19. The pooled analysis showed higher D-dimer levels in the severe COVID-19 group compared with the nonsevere group (mean difference, 1.88; 95% CI, 0.49–3.27; *P* = 0.008; I^2 = 100%; Supplementary material). A higher level of D-dimer was also observed in the intensive care unit patients compared with non-ICU patients (MD, 1.13; 95% CI, 0.69–1.57; *P* <0.001; I^2 = 97%) and in patients who died as compared with those who survived (MD, 3.54; 95% CI, 2.57–4.52; *P* <0.001; I^2 = 99%; Supplementary material). The full list of publications included in this meta-analysis is presented in the Supplementary material.

In conclusion, our analysis showed that elevated D-dimer levels were associated with increased odds of developing severe disease and increased odds of mortality in patients with COVID-19.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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Authors' reply We read with great interest the study by Ruetzler et al[1] who interpreted the importance of D-dimers in SARS-CoV-2 infection in reference to the synthetic summary of the current knowledge on the various aspects of heart failure in patients with coronavirus disease 2019 (COVID-19).[2]

As it was previously shown, markedly elevated D-dimer levels are related to a poor prognosis.[1,3] In SARS-CoV-2 infection, an increased uncontrolled inflammatory response with a cytokine storm is the most frequent observation. However, also a variety of pathophysiological derangements, including pulmonary inflammation and (micro)-thrombosis that may also spill over into the systemic circulation can be observed.[3,4] Both hyperinflammation and coagulopathy are in turn associated with a wide derangement in various hemostasis parameters, including D-dimer, prothrombin time, and thrombocytopenia. All of them may serve as potential prognostic markers of disease severity and/or mortality[3].

Initially, the elevation of plasma D-dimers was considered as indicator of coagulopathy, related to the accelerated fibrinolysis due to an increased thrombin generation, indeed an indication of disseminated intravascular coagulation. However, D-dimer levels are elevated alongside other acute inflammatory plasma markers such as fibrinogen, C-reactive protein, and serum ferritin.[1] Therefore, an alternative hypothesis was proposed, which suggests that the origin of D-dimers is a direct consequence of the acute lung injury seen in COVID-19 pneumonia.[5]

However, it is important that intra-alveolar fibrin deposition is the hallmark of acute lung injury. The levels of fibrin are controlled by alveolar epithelial cells which produce urokinase and regulate extravascular proteolysis by regulating expression of urokinase-type plasminogen activator, its receptor, and plasminogen activator inhibitor-1 at post-transcriptional levels.[5] Urokinase then converts plasminogen to plasmin, which cleaves local fibrin.[5] Based on the above evidence, we suggest that D-dimer levels are not only related to coagulopathy but also, similarly to other acute-phase proteins such as C-reactive protein, ferritin, and fibrinogen, with the severity of COVID-19, represent the degree of lung inflammation in SARS-CoV-2 infection.[5]

In addition, the analysis of the single biochemical parameter must be interpreted very carefully, especially in the context of cardiovascular complications of SARS-CoV-2 infection. Only the complex analysis of clinical state as well as imaging and biochemical tests can provide valuable information about organ and systemic consequences, and indicate particularly vulnerable patient subgroups and be useful in choosing the most beneficial therapy.

Moreover, the interpretation of D-dimers levels is limited due to several factors. There is no single standardized D-dimer assay, which leads to a potential bias in reporting D-dimer levels and is associated with considerable variation in reporting units for that parameter. Also, potential misrepresentation of D-dimer data due to poor or incomplete reporting is possible.

The study by Ruetzler et al[1] presented analysis based mostly on retrospective studies covering limited populations, which may affect the overall understanding of the results and their interpretation. SARS-CoV-2 infection is a very complex process and therefore requires a multimodality approach. It is very important that the interpretation of individual tests, including D-dimer levels, is made in the context of the patient's clinical state. The factors connecting with the poor prognosis of COVD-19 are constantly being discovered, but it is definitely not a single parameter.

Finally, concluding on the clinical level, it is important to remember that the risk of thrombosis in critically ill patients is high and thrombotic events occur despite the prophylactic use of low-molecular-weight heparin. Therefore, there is an urgent need for the results from randomized trials regarding the appropriate antithrombotic prophylaxis and treatment.

ARTICLE INFORMATION

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